Chromosome segregation model - detailed description

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Introduction

This is a more detailed version of the kinetochore segregation model to be published in the JCB article, which should be referred to for all the experimental, biological and non-technical aspects of this work.

1 Definitions

1.1 State vector

The mitotic spindle is described by the speeds and position along the x axis of two spindle pole bodies, N chromosomes with two centromeres and M_k attachment sites per centromere.

Positions are noted as follow:

- The left and right spindle pole bodies (SPBs), x_s^L and x_s^R
- The N centromeres, x_n^A, $x_n^B, n \in \{1, \cdots, N\}$
- The M_k attachment sites of each centromere, x_{nm}^A, $x_{nm}^B, n \in \{1, \cdots, N\}, m \in \{1, \cdots, M_k\}$

The speeds are noted with a dot: $dx/dt = \dot{x}$.

As all the interactions are assumed to be parallel to the spindle axis, only the positions along this axis are considered, in a coordinate system with its origin at the center of the spindle, which means that $x_s^L(t) = -x_s^R(t)\,\forall t$.

1.2 Random variables for the attachment

We define ρ_{nm}^A and λ_{nm}^A, two random variables that govern the attachment state of the site x_{nm}^A, such that:

$$\rho_{nm}^A = \begin{cases} 1 & \text{if the site is attached to the right SPB} \\ 0 & \text{otherwise} \end{cases} \tag{1}$$

$$\lambda_{nm}^A = \begin{cases} 1 & \text{if the site is attached to the left SPB} \\ 0 & \text{otherwise} \end{cases} \tag{2}$$

Note that ρ_{nm}^A and λ_{nm}^A are not independent, as an attachment site can't be attached to both poles. To take this into account, we can define the variable $\pi_{nm}^A = \rho_{nm}^A - \lambda_{nm}^A$ such that:

$$\pi_{nm}^A = \begin{cases} -1 & \text{if the site is attached to the left SPB} \\ 0 & \text{if the site is not attached} \\ 1 & \text{if the site is attached to the right SPB} \end{cases} \tag{3}$$

We have:

$$\lambda_{nm}^{A} = \pi_{nm}^{A}\left(\pi_{nm}^{A} - 1\right)/2 \tag{4}$$
$$\rho_{nm}^{A} = \pi_{nm}^{A}\left(\pi_{nm}^{A} + 1\right)/2 \tag{5}$$

We also define N_n^{AL} and N_n^{AR} as the number of ktMTs of centromere A attached to the left and right SPBs, respectively:

$$N_n^{AL} = \sum_{m=1}^{M_k} \lambda_{nm}^{A} \text{ and } N_n^{AR} = \sum_{m=1}^{M_k} \rho_{nm}^{A} \tag{6}$$

Note that $N_n^{AL} + N_n^{AR} \leqslant M_k \, \forall \, \pi_{nm}$ The same definitions apply for the centromere B and left SPB.

1.3 Forces

The following force balances are considered:

1.3.1 Forces at the right SPB :

- Friction forces (viscous drag): $F_f^R = -\mu_s \dot{x_s}^R$
- Midzone force generators:

$$F_{mid} = F_z\left(1 - (\dot{x}_s^R - \dot{x}_s^L)/V_z\right) = F_z\left(1 - 2\dot{x}_s^R/V_z\right)$$

- Total kinetochore microtubules force generators:

$$\begin{aligned} F_{kMT}^{T} = \sum_{n=1}^{N}\sum_{m=1}^{M_k} & - \rho_{nm}^{A}\, F_k\left(1 - (\dot{x}_{nm}^{A} - \dot{x}_s^R)/V_k\right) \\ & - \rho_{nm}^{B}\, F_k\left(1 - (\dot{x}_{nm}^{B} - \dot{x}_s^R)/V_k\right) \end{aligned}$$

1.3.2 Forces at the left SPB :

Because of the reference frame definition, $\dot{x_s}^R = -\dot{x_s}^L \, \forall t$. Here we substituted x_s^L with $-x_s^R$

- Friction forces (viscous drag): $F_f^L = \mu_s \dot{x_s}^R$
- Midzone force generators:

$$F_{mid}^{L} = -F_z\left(1 - 2\dot{x}_s^R/V_z\right)$$

- Total kinetochore microtubules force generators:

$$\begin{aligned} F_{kMT}^{T} = \sum_{n=1}^{N}\sum_{m=1}^{M_k} & - \lambda_{nm}^{A}\, F_k\left(1 + (\dot{x}_{nm}^{A} + \dot{x}_s^R)/V_k\right) \\ & - \lambda_{nm}^{B}\, F_k\left(1 + (\dot{x}_{nm}^{B} + \dot{x}_s^R)/V_k\right) \end{aligned}$$

1.3.3 Forces at centromere An

- Drag: $F_c^f = -\mu_c \dot{x_n}^A$
- Cohesin bond (Hook spring) restoring force exerted by centromere[1]:

$$F_{BA} = \begin{cases} \kappa_c(x_n^B - x_n^A - d_0) & \text{if} \quad d_0 < x_n^A - x_n^B \\ 0 & \text{if} \quad -d_0 < x_n^A - x_n^B < d_0 \\ \kappa_c(x_n^B - x_n^A + d_0) & \text{if} \quad x_n^A - x_n^B \end{cases} \tag{7}$$

With $F_{AB} = -F_{BA}$.

- Total visco-elastic bond between the centromere A and the attachment sites:

$$F_v^T = \sum_{m=1}^{M_k} -\kappa_k(x_n^A - x_{nm}^A) - \mu_k(\dot{x}_n^A - \dot{x}_{nm}^A)$$

1.3.4 Forces at attachment site Anm

- Visco-elastic bond between the centromere A and the attachment sites:

$$F_v = \kappa_k(x_n^A - x_{nm}^A) + \mu_k(\dot{x}_n^A - \dot{x}_{nm}^A)$$

- Kinetochore microtubules force generators:

$$\begin{aligned} F_{kMT}^A &= F_{kMT}^{RA} + F_{kMT}^{LA} \\ F_{kMT}^{RA} &= \rho_{nm}^A \, F_k \left(1 - \frac{\dot{x}_{nm}^A - \dot{x}_s^R}{V_k}\right) \\ F_{kMT}^{LA} &= \lambda_{nm}^A \, F_k \left(-1 - \frac{\dot{x}_{nm}^A - \dot{x}_s^L}{V_k}\right) \end{aligned} \tag{8}$$

With $F_k = 1$ and $V_k = 1$ (for now on, we are taking F_k as unit force and V_k as unit speed), this gives:

$$F_{kMT}^A = \rho_{nm}^A \left(\dot{x}_s^R - \dot{x}_{nm}^A + 1\right) - \lambda_{nm}^A \left(\dot{x}_s^R + \dot{x}_{nm}^A + 1\right) \tag{9}$$

Eventually, substituting $\lambda_{nm}^A - \rho_{nm}^A$ with π_{nm}^A and $\lambda_{nm}^A + \rho_{nm}^A$ with $|\pi_{nm}^A|$:

$$F_{kMT}^A = \pi_{nm}^A(\dot{x}_s^R + 1) - |\pi_{nm}^A|\dot{x}_{nm}^A \tag{10}$$

1.4 Set of first order coupled equations

In the viscous nucleoplasm, inertia is negligible. Newton first principle thus reduces to: $\sum F = 0$. This force balance equation can be written for each elements of the spindle. To simplify further, the equations for the right and left SPBs can be combined:

$$\begin{aligned} -\mu_s \dot{x}_s^R + F_z\left(1 - 2\dot{x}_s^R/V_z\right) + \sum_{n,m} -\rho_{nm}^A \left(\dot{x}_s^R - \dot{x}_{nm}^A + 1\right) &= 0 \text{ for the right SPB} \\ \mu_s \dot{x}_s^R - F_z\left(1 - 2\dot{x}_s^R/V_z\right) + \sum_{n,m} \lambda_{nm}^A \left(\dot{x}_s^R + \dot{x}_{nm}^A + 1\right) &= 0 \text{ for the left SPB} \end{aligned} \tag{11}$$

[1]We want the centromeres to be able to cross each over. In one dimension, this introduces a discontinuity. In the previous version, the 'swap' mechanism was solving this directly (as x_A and x_B are exchanged). This is not possible any more, as the 'swap' mechanism is now irrelevant, as there is no prefered side for a given centromere. With this model, the discontinuity is only to the first order. I am convinced there can be a better regularisation.

The difference of those two expressions gives, with the same substitutions as before:

$$- 2\mu_s \dot{x}_s^R + 2F_z \left(1 - 2\dot{x}_s^R / V_z\right) + \sum_{n,m} -(|\pi_{nm}^A| + |\pi_{nm}^B|)(\dot{x}_s^R + 1) + \pi_{nm}^A \dot{x}_{nm}^A + \pi_{nm}^B = 0 \tag{12}$$

All the equations are gathered together in the system of equations:

$$\mathbf{A}\dot{X} + \mathbf{B}X + C = 0$$

The vector X has $1 + 2N(M_k + 1)$ elements and is defined as follow[2]:

$$X = \{x_s^R, \{x_n^A, \{x_{nm}^A\}, x_n^B, \{x_{nm}^B\}\}\} \text{ with } n \in 1 \cdots N \text{ and } m \in 1 \cdots M_k$$

In matrix form, we have:

$$X = \begin{pmatrix} x_s^R \\ x_n^A \\ x_{nm}^A \\ x_n^B \\ x_{nm}^B \end{pmatrix} = \begin{pmatrix} \text{Right SPB} \\ \text{Centromere } A, n \\ \text{Attachment site } A, n, m \\ \text{Centromere } B, n \\ \text{Attachment site } B, n, m \end{pmatrix}$$

$$A = \begin{pmatrix} -2\mu_s - 4F_z/V_z - \sum(|\pi_{nm}^A| + |\pi_{nm}^B|) & \dots & \pi_{nm}^A & \dots & \pi_{nm}^B \\ \dots & -\mu_c - M_k\mu_k & \mu_k & \dots\dots\dots & \\ \pi_{nm}^A & \mu_k & -\mu_k - |\pi_{nm}^A| & \dots\dots\dots & \\ \dots\dots\dots & & & -\mu_c - M_k\mu_k & \mu_k \\ \pi_{nm}^B & \dots\dots\dots & & \mu_k & -\mu_k - |\pi_{nm}^B| \end{pmatrix},$$

$$B = \begin{pmatrix} 0 & \dots\dots\dots & & & \\ \dots & -|\delta_n^{AB}|\kappa_c - M_k\kappa_k & \kappa_k & |\delta_n^{AB}|\kappa_c & \dots \\ \dots & \kappa_k & -\kappa_k & \dots\dots\dots & \\ \dots & |\delta_n^{AB}|\kappa_c & \dots & -|\delta_n^{AB}|\kappa_c - M_k\kappa_k & \kappa_k \\ \dots\dots\dots & & & \kappa_k & -\kappa_k \end{pmatrix}$$

$$C = \begin{pmatrix} 2Fz - \sum_{n,m}(|\pi_{nm}^A| + |\pi_{nm}^B|) \\ \delta_n^{AB}\kappa_c d_0 \\ \pi_{nm}^A \\ -\delta_n^{AB}\kappa_c d_0 \\ \pi_{nm}^B \end{pmatrix} \text{ with } \delta_n^{AB} = \begin{cases} 1 & \text{if} \quad d_0 < x_n^A - x_n^B \\ 0 & \text{if} \quad -d_0 < x_n^A - x_n^B < d_0 \\ -1 & \text{if} \quad x_n^A - x_n^B \end{cases} \tag{13}$$

As is actually done in the python implementation, A can be decomposed into a time invariant part A_0 and a variable part A_t with:

$$A_0 = \begin{pmatrix} -2\mu_s - 4F_z/V_z & \dots\dots\dots & & & \\ \dots & -\mu_c - M_k\mu_k & \mu_k & \dots\dots\dots & \\ \dots & \mu_k & -\mu_k & \dots\dots\dots & \\ \dots\dots\dots & & & -\mu_c - M_k\mu_k & \mu_k \\ \dots\dots\dots & & & \mu_k & -\mu_k \end{pmatrix}$$
$$A_t = \begin{pmatrix} -\sum(|\pi_{nm}^A| + |\pi_{nm}^B|) & \dots & \pi_{nm}^A & \dots & \pi_{nm}^B \\ \dots\dots\dots & & & & \\ \pi_{nm}^A & \dots & -|\pi_{nm}^A| & \dots\dots\dots & \\ \dots\dots\dots & & & & \\ \pi_{nm}^B & \dots\dots\dots & & & -|\pi_{nm}^B| \end{pmatrix} \tag{14}$$

[2]Note that the left SPB is omitted in X.

Equivalently for B:

$$B_0 = \begin{pmatrix} 0 & \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \\ \ldots & -M_k\kappa_k & \kappa_k & \ldots\ldots\ldots\ldots \\ \ldots & \kappa_k & -\kappa_k & \ldots\ldots\ldots\ldots \\ \ldots & \ldots\ldots\ldots\ldots & -M_k\kappa_k & \kappa_k \\ \ldots\ldots\ldots\ldots\ldots\ldots & & \kappa_k & -\kappa_k \end{pmatrix} = \kappa_k \begin{pmatrix} 0 & \ldots\ldots\ldots\ldots\ldots\ldots\ldots \\ \ldots & -M_k & 1 & \ldots\ldots\ldots \\ \ldots & 1 & -1 & \ldots\ldots\ldots \\ \ldots & \ldots\ldots\ldots & -M_k & 1 \\ \ldots\ldots\ldots\ldots\ldots & & 1 & -1 \end{pmatrix} \tag{15}$$

And

$$B_t = \kappa_c \begin{pmatrix} 0 & \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \\ \ldots & -|\delta_n^{AB}| & \ldots & |\delta_n^{AB}| & \ldots \\ \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \\ \ldots & |\delta_n^{AB}| & \ldots & -|\delta_n^{AB}| & \ldots \\ \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \end{pmatrix} \tag{16}$$